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(54) Title: TREATMENT FOR CRYOPYRIN ASSOCIATED PERIODIC SYNDROMES (CAPS)

(57) **Abstract:** Present invention relates to development of compound of formula (I) for treatment of Cryopyrin Associated Periodic Syndromes (CAPS). Specifically, the present invention provides a NLRP3 inhibitors or its pharmaceutically acceptable salt for treatment of Cryopyrin Associated Periodic Syndromes (CAPS). Invention also relates to the pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts for treatment of Cryopyrin Associated Periodic Syndromes (CAPS).



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TREATMENT FOR CRYOPYRIN ASSOCIATED PERIODIC SYNDROMES (CAPS)

FIELD OF THE INVENTION

Present invention relates to development of compound of formula (I) for treatment of Cryopyrin Associated Periodic Syndromes (CAPS). Specifically, the present invention provides a NLRP3 inhibitors or its pharmaceutically acceptable salt for treatment of Cryopyrin Associated Periodic Syndromes (CAPS). Invention also relates to the pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts for treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

BACKGROUND OF THE INVENTION

The nucleotide-binding oligomerization domain (NOD)-like receptor family, pyrin domain-containing 3 (NLRP3 or NALP3) inflammasome are a major source of mucosal interleukin (IL)-1 β and the inflammasomes are mostly subject to activation by multiple aspects of inflammation-associated stress. NLRP3 is a cytosolic pattern recognition receptor (PRR) that senses exogenous and endogenous danger signals. The NLRP3 protein is made up of three domains: a leucine-rich repeat domain (LRR), a NOD containing a caspase activation and recruitment domain (CARD) (NACHT), and a pyrin domain (PYD). Upon activation, NLRP3 oligomerizes and triggers assembly of the adapter apoptosis-associated speck-like protein containing a CARD (ASC) via PYD–PYD interactions. ASC fibrils assemble into large structures, called ASC specks, and recruit pro-caspase-1, leading to its autoproteolytic activation. The activated caspase-1 is able to cleave pro-IL-1 β and pro-IL-18 to generate the inflammatory cytokines IL-1 β and IL-18 (Guo et al., 2015; Dinarello et al., 2012).

Involvement of the NLRP3 inflammasome in different kinds of diseases provides new avenues to design drugs targeting NLRP3 inflammasome. To date, clinical treatment of NLRP3-related diseases targets IL-1 β with IL-1 β antibodies or recombinant IL-1 β receptor antagonist, such as canakinumab and anakinra, respectively. In addition, a few small-

molecule compounds have shown anti-inflammatory effects on NLRP3 inflammasome activation in vitro, including MCC950, β -hydroxybutyrate (BHB), Bay 11-7082, dimethyl sulfoxide (DMSO), and type I interferon. However, most of these inhibitors are relatively nonspecific and have low efficacy. For inhibitors targeting IL-1 β , it should be noted that

5 IL-1 β secretion is not the only product of NLRP3 inflammasome activation; instead, other pro-inflammatory cytokines, including high-mobility group box 1 (HMGB1) and IL-18 may participate in the pathogenesis of these diseases. Moreover, IL-1 β can be produced by inflammasome-independent pathways or other inflammasomes. Therefore, inhibitors targeting IL-1 β may lead to unintended immunosuppressive effects besides preventing

10 NLRP3 inflammasome activation itself. Pharmacological inhibitors specific to NLRP3 inflammasome may be the best choice for treatment of NLRP3-related diseases. (Yang et al., 2019).

Cryopyrin-associated periodic syndromes (CAPs) are a rare family of heterogeneous autoinflammatory diseases characterized by IL-1 β -mediated systemic inflammation and

15 clinical symptoms involving skin, joints, central nervous system and eyes. CAPS is associated with an activating mutation in NLRP3, of which approximately 200 mutations have been defined. While some mutations have been classed as benign and present with no deleterious clinical phenotype, approximately 100 of the reported mutations result in a chronic pro-inflammatory presentation. CAPS is categorized into three clinical subgroups

20 of increasing severity: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurologic cutaneous and articular syndrome or CINCA) (Booshehri et al., 2019). Mice that harbour the mutant forms of NLRP3 that occur in CAPS die in the neonatal period and have increased concentrations of circulating IL-1 β and IL-18

25 (Coll *et al.* 2015). Previously demonstrated that MCC950 inhibited NLRP3 activation in a mouse model of MWS. Peripheral blood mononuclear cells (PBMC) from patients with low penetrance NLRP3 variants (Q703K and V198M) have been shown to display enhanced IL-1 β levels following inflammasome activation compared to healthy controls. Furthermore, release of IL-1 β has been shown to be NLRP3-dependent as it was blocked by MCC950

(Schuh et al., 2019). The IL-1 receptor antagonist anakinra is conventionally used to control the symptoms of the syndrome, but patients relapse when treatment is withdrawn.

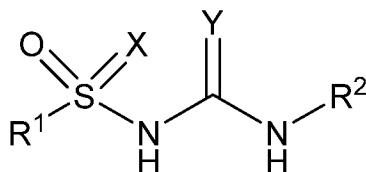
There are various agents in various stages of Phase I and Phase II development that target the NLRP3 inflammasome. (Freeman et al., 2020). Agents like MCC950, CY-09, OLT1177, Tranilast, Oridonin, NT-0167 displayed the good therapeutic properties, as they directly target NLRP3 itself, but not other components (NEK7, ASC, caspase-1, or IL-1 β) up-/downstream of NLRP3 inflammasome activation. Furthermore, these inhibitors are being used in clinical practice are being investigated at phase II clinical trials having shown relatively high safety (Yang et al., 2019).

- 10 NLRP3 in innate immune cells are activated by Pathogen Associated Molecular Patterns and Death Associated Molecular Patterns. The resultant NLRP3 inflammasome activates Caspase-1 and in-turn cleave and releases IL-1 β and IL-18. NLRP3 inflammasome inhibitors have potential to negate IL-1 mediated disease pathologies including CAPS.

- 15 All current therapies are limited to injectable biologics that often have limited central nervous system (CNS) penetration, which is particularly important in NOMID patients with severe CNS disease. Therefore, there remains an unmet clinical need for more targeted, and preferably small molecule, compounds as an alternative to IL-1 targeted biologics.

EMBODIMENTS OF THE INVENTION

- 20 In an embodiment, the present invention provides a therapeutic compound of formula (I) or its pharmaceutically acceptable salts suitable for the treatment and prevention of Cryopyrin Associated Periodic Syndromes (CAPS).



Formula (I)

In another embodiment, the present invention provides pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts and pharmaceutically acceptable excipients for the treatment and prevention of Cryopyrin Associated Periodic Syndromes (CAPS).

- 5 In yet another embodiment, the present invention provides the administration of therapeutic compound of formula (I) and their pharmaceutically acceptable salts alone or in combination with suitable for the treatment and prevention of Cryopyrin Associated Periodic Syndromes (CAPS).

- 10 In a further embodiment, the present invention provides use of compound of formula (I) or its pharmaceutically acceptable salts for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In another embodiment, the present invention provides a method of treating Cryopyrin Associated Periodic Syndromes (CAPS) using pharmaceutical composition of compound of formula (I) or its pharmaceutically acceptable salts.

- 15 The above and other embodiments of the present invention are disclosed further hereinafter.

SUMMARY OF THE INVENTION

- The present invention provides a therapeutic compound of formula (I) or its pharmaceutically acceptable salts for the prevention and treatment of Cryopyrin Associated Periodic Syndromes (CAPS) and related diseases. Present invention also relates to
20 pharmaceutical composition comprising compound of formula (I) or pharmaceutically acceptable excipients useful for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

DETAIL DESCRIPTION OF THE INVENTION

Definition:

The terms 'treatment' or 'treat' refer to slowing, stopping, or delaying the progression of the disease or clinical symptoms in a patient, as evidenced by a decrease or elimination of a clinical or diagnostic symptom of the disease, disorder or condition.

The term 'subject' refer to a mammals.

- 5 The term 'effective amount' in the context of the administration of the amount of the drug substance sufficient to have the desired effect.

"Patient" includes both human and animals. "Mammal" means humans and other mammalian animals.

- 10 The term "preventing" refers to barring a subject from acquiring a disorder or disease in the first place.

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

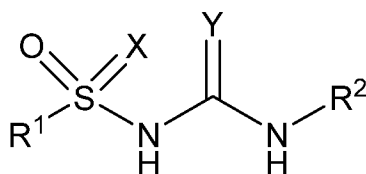
- 15 As used herein "treating" includes achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome. Delaying, inhibiting or preventing the progression of the disease, disorder or syndrome includes for example, delaying, inhibiting or preventing the progression of. Cryopyrin Associated Periodic Syndromes (CAPS).

- 20 The present invention describes a method of treating a subject suffering from Cryopyrin Associated Periodic Syndromes (CAPS).

In an embodiment the present invention provides a compound of formula (I) or its pharmaceutically acceptable salts suitable for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In a further embodiment the present invention provides use of the compound of formula (I) or their suitable pharmaceutical compositions for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

The method comprises administering to a subject an effective amount of a compound according to Formula (I),



Formula (I)

their tautomeric forms, their stereoisomers; their enantiomers; their metabolites; their deuterium analogs; their pharmaceutically acceptable salts; and pharmaceutical compositions containing them or their mixtures thereof, wherein

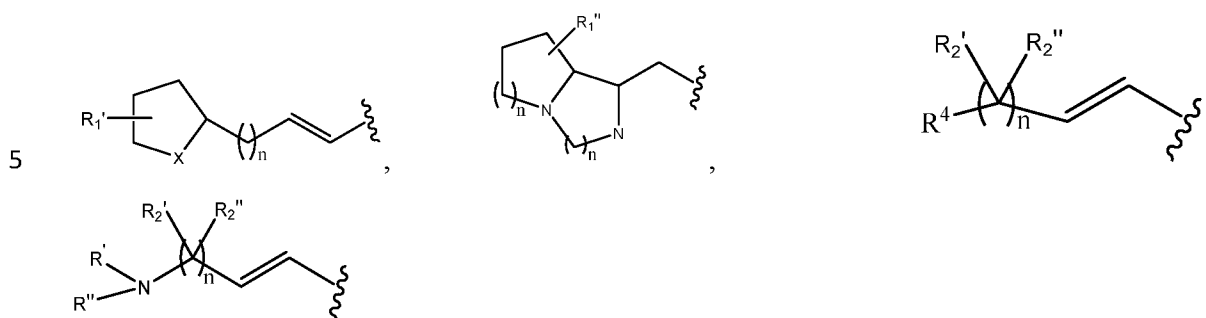
X is O, NH, or N-R³ wherein R³ at each occurrence independently represents hydrogen, hydroxyl, halogen, nitro, cyano, haloalkyl, optionally substituted groups selected from (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₃-C₁₀)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, SO₂(C₁-C₆)alkyl, thiol, thioalkyl, thio-alkoxy, SO(C₁-C₆)alkyl, benzyl, aryl, heteroaryl, heterocyclyl;

Y is O, S;

R¹ at each occurrence independently represents hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₃-C₇)cycloalkyl, (C₁-C₆)alkylSO₂(C₁-C₆)alkyl, (C₁-C₆)alkylN(C₁-C₆)alkyl, (C₁-C₆)alkylN(C₃-C₇)cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, tert-butyloxycarbonyl, NH(C₁-C₆)alkyl, N((C₁-C₆)alkyl)₂, NH(C₂-C₆)alkenyl, N((C₂-C₆)alkenyl)₂, -N-heterocyclyl, N(C₁-C₆)alkyl-heterocyclyl, NR'R'', thiol, mercaptoalkyl, SO₂(C₁-C₆)alkyl, SO₂(C₃-C₇)cycloalkyl, SO₂-aryl, SO₂-heterocyclyl, (C₁-C₆)thioalkyl, (C₁-C₆)thioalkoxy, (C₁-C₆)alkylSO₂NH₂, -CONH₂, -CO(C₁-C₆)alkyl, -CO(C₁-

C₆)haloalkyl, -CO-aryl, -CO-heteroaryl, -CO-heterocyclyl, 4- to 7-membered heterocyclic ring, 7- to 14-membered bicyclic heterocyclic ring system, bridged or spiro ring system having optionally one or more than one heteroatoms;

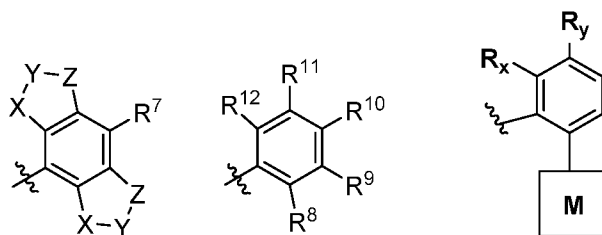
In an embodiment R¹ represents:



n, is independently selected from integer 0-3;

each of R¹, R², R^{1'}, R^{1''}, R^{2'} and R^{2''} at each occurrence independently represents hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₃-C₇)cycloalkyl, (C₁-C₆)alkylSO₂(C₁-C₆)alkyl, (C₁-C₆)alkylN(C₁-C₆)alkyl, (C₁-C₆)alkylN(C₃-C₇)cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, tert-butyloxycarbonyl, thiol, mercaptoalkyl, SO₂(C₁-C₆)alkyl, SO₂(C₃-C₇)cycloalkyl, SO₂-aryl, SO₂-heterocyclyl, (C₁-C₆)thioalkyl, (C₁-C₆)thioalkoxy, (C₁-C₆)alkylSO₂NH₂, -CONH₂, -CO(C₁-C₆)alkyl, -CO(C₁-C₆)haloalkyl, -CO-aryl, -CO-heteroaryl, -CO-heterocyclyl, 4- to 7-membered heterocyclic ring, 7- to 14-membered bicyclic heterocyclic ring system, bridged or spiro ring system having optionally one or more than one heteroatoms; In an embodiment R¹ and R² optionally forms 4- to 7-membered heterocyclic ring system.

R² is selected from the following ring system



wherein X, Y, Z at each occurrence independently represents C, N, S, SO₂, and O, which may be optionally substituted;

each of R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² at each occurrence are independently selected from hydrogen, halogen, cyano, amide, sulphonamide, acyl, hydroxyl, optionally substituted groups selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, benzyl, aryl, heteroaryl, heterocyclyl; In one embodiment each of R⁸ and R⁹, R⁹ and R¹⁰, R¹⁰ and R¹¹ and R¹¹ and R¹² wherever possible, together may form a 4 to 7 membered saturated or partially saturated ring containing from 0-2 additional heteroatoms selected from the group consisting of N, O, and S(O)_p; p = 1-2.

- 10 R_x and R_y at each occurrence are independently selected from hydrogen, halogen, optionally substituted groups selected from (C₁-C₆)alkyl; Alternatively R_x and R_y together may form a 4- to 7-membered heterocyclic ring system;

'M' is selected from aryl, heteroaryl, heterocyclyl;

- When any of above defined group is substituted the substitutions on them may be selected from those described above or may be selected from hydrogen, hydroxy, cyano, halo, haloalkyl, haloalkyloxy, alkylthio, optionally substituted group selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₁₀)cycloalkyl, C₁-C₆ alkoxy, aryl, heterocyclyl, heteroaryl, -COR₁₁, -CSR₁₁, C(O)OR₁₁, C(O)-R₁₁, -C(O)-NR₁₁R₁₂, -C(S)-NR₁₁R₁₂, -SO₂R₁₁ group, wherein each of, R₁₁ and R₁₂ is independently selected from hydrogen, optionally substituted group selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)cycloalkyl, aryl, heteroaryl, heterocyclyl groups;

In a preferred embodiment, the groups, radicals described above may be selected from:

- "Alkyl", as well as other groups having the prefix "alk", such as alkoxy and alkanoyl, means a carbon chain which may further be substituted with an oxygen atom as is well understood by a skilled artisan, which may further be either linear or branched, and combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl group include but not limited to methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert. -

butyl, pentyl, hexyl etc. Where the specified number of carbon atoms permits e.g. from C₃₋₁₀, the term alkyl also includes cycloalkyl groups, and combinations of linear or branched alkyl chains combined with cycloalkyl structures. When no number of carbon atoms is specified, C₁₋₆ is intended. Substituted alkyl includes alkyl substituted with one or more
5 moieties selected from the group consisting of halo {e.g., Cl, F, Br, and I}; halogenated alkyl {e.g., CF₃, 2-Br-ethyl, CH₂F, CH₂Cl, CH₂CF₃, or CF₂CF₃}; hydroxyl; amino; carboxylate; carboxamido; alkylamino; arylamino; alkoxy; aryloxy; nitro; azido; cyano; thio; sulfonic acid; sulfate; phosphonic acid; phosphate; and phosphonate as well as those described under the definition of 'Optionally substituted'.

10 "Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Examples of alkenyl include but not limited to vinyl, allyl, isopropenyl, hexenyl, pentenyl, heptenyl, 1 -propenyl, 2-butenyl, 2-methyl -2-butenyl etc. Where the specified number of carbon atoms permits, e.g., from C₅₋₁₀, the term alkenyl also includes
15 cycloalkenyl groups and combinations of linear, branched and cyclic structures. When no number of carbon atoms is specified, C₂₋₆) is intended.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl- 1 -pentynyl etc. When no number of carbon atoms is
20 specified, is intended.

the "thioalkyl" group used either alone or in combination with other radicals, denotes an alkyl group, as defined above, attached to a group of formula -SR', (sulfur and its oxidized forms) where R' represents hydrogen, alkyl or aryl group, e.g. thiomethyl, methylthiomethyl, phenylthiomethyl and the like, which may be optionally substituted.

25 As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable monocyclic or bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,

[3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). In a broader perspective, the term carbocycle is intended to include, wherever applicable, the groups representing cycloalkyl, phenyl and other saturated, partially saturated or aromatic residues;

The terms "cycloalkyl" and "cycloalkenyl" refers to optionally substituted, saturated and unsaturated mono-cyclic, bicyclic or tricyclic carbon groups. Where appropriate, the cycloalkyl or cycloalkenyl group may have a specified number of carbon atoms, for example, C₃-C₆ cycloalkyl or cycloalkenyl includes within its scope a carbocyclic group having 3, 4, 5 or 6 carbon atoms. Examples of such substituents may be selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and the like. Substituted cycloalkyl or cycloalkenyl includes substitutions with one or more moieties selected from the group consisting of halo (e.g. , Cl, F, Br, and I); halogenated alkyl (e.g. , CF₃, 2-Br-ethyl, CH₂F, CH₂Cl, CH₂CF₃, or CF₂CF₃); hydroxyl; amino; carboxylate; carboxamido; alkylamino; arylamino; alkoxy; aryloxy; nitro; azido; cyano; thio; sulfonic acid; sulfate; phosphonic acid; phosphate; and phosphonate as well as those described under the definition of 'Optionally substituted'.

The "alkoxy" refers to the straight or branched chain alkoxides of the number of carbon atoms specified.

"Aryl" means a mono- or polycyclic aromatic ring system containing carbon ring atoms. The preferred aryls are monocyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls.

"Heterocyclyl" means a saturated, partially saturated or unsaturated aromatic or non-aromatic mono, bi or tricyclic radicals, containing one or more heteroatoms selected from nitrogen, sulfur and oxygen, further optionally including the oxidized forms of sulfur, namely SO & SO₂. Heterocyclyl systems may be attached to another moiety via any number of carbon atoms or heteroatoms of the radical and may be both saturated and unsaturated. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane,

morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazoline, imidazolidine, pyrrolidine, pyrroline, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, etc. The term "heterocycloalkyl" refers to a heterocyclic group as defined above connected to an alkyl group as defined above;

"Heteroaryl" means an aromatic or partially aromatic heterocycle that contains at least one ring heteroatom selected from O, S and N. Heteroaryls thus include heteroaryls fused to other kinds of rings, such as aryls, cycloalkyls, and heterocycles that are not aromatic. Examples of heteroaryl groups include; pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, triazinyl, thienyl, pyrimidyl, benzisoxazolyl, benzoxazolyl, benzthiazolyl, benzothiadiazolyl, dihydrobenzofuranyl, indolyl, pyridazinyl, indazolyl, isoindolyl, dihydrobenzothienyl, indolyl, pyridazinyl, indazolyl, isoindolyl, dihydrobenzothienyl, indolizyl, cinnolyl, phthalazinyl, quinazolinyl, naphthyridinyl, carbazolyl, benzodioxolyl, quinoxalinyl, purinyl, furazanyl, isobenzylfuranyl, benzimidazolyl, benzofuranyl, benzothienyl, quinolyl, indolyl, isoquinolyl, dibenzofuranyl etc. For heterocyclyl; and heteroaryl groups, rings and ring systems containing from 3-15 carbon atoms are included, forming 1-3 rings.

The term "haloalkyl" means an alkyl structure in which at least one hydrogen is replaced with a halogen atom. In certain embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are all the same as one another.

the "haloalkoxy" group is selected from suitable haloalkyl, as defined above, directly attached to an oxygen atom, more preferably groups selected from fluoromethoxy, chloromethoxy, fluoroethoxy, chloroethoxy and the like;

In certain other embodiment in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are not all the same as one another.

"Aryloxyalkyl" means an alkyl radical substituted with aryloxy group as defined herein.

"Aryloxyaryl" means an aryl radical substituted with aryloxy group as defined herein.

"Aryloxyheteroaryl" means a heteroaryl radical substituted with aryloxy group as defined herein.

5 "Halo/ Halogen" refers to fluorine, chlorine, bromine, iodine. Chlorine and fluorine are generally preferred.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

10 The term "substituted," as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound.

15 "Pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of the basic residues. Such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 1, 2-ethanedisulfonic, 2-acetoxybenzoic, 2-hydroxyethanesulfonic, acetic, ascorbic, benzenesulfonic, benzoic, 20 bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, -lauryl sulfonic, maleic, malic, mandelic, methanesulfonic, napsylic, 25 nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluenesulfonic.

The term 'optional' or 'optionally' means that the subsequent described event or circumstance may or may not occur, and the description includes instances where the event or circumstance occur and instances in which it does not. For example, optionally substituted alkyl' means either 'alkyl' or 'substituted alkyl'. Further an optionally substituted group includes an unsubstituted group.

Unless otherwise stated in the specification, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms.

Particularly useful compounds may be selected from but not limited to the following:

10 N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide;

N'-cyano-4-fluoro-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide;

15 N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide;

(E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(thiazol-2-yl)ethenesulfonamide;

(E)-2-(1-ethyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide;

20 (E)-2-(1-ethyl-4-methyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide;

(R,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide;

25 (R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-methylpyrrolidin-2-yl)ethene-1-sulfonamide;

(S,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide;

(R,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

5 (S,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

sodium(S,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

10 potassium (R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

Sodium(R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

(E)-N'-cyano-2-((S)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide;

15 (E)-N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-((R)-1-methylpyrrolidin-2-yl)ethene-1-sulfonimidamide;

20 (E)-N'-cyano-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide;

N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((1S,8aR)-3,3,8a-trimethyloctahydropyrrolo[1,2-a]pyrazin-1-yl)methanesulfonamide;

25 N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((4S,8aS)-2,3,3,8a-tetramethyloctahydropyrrolo[1,2-a]pyrazin-4-yl)methanesulfonamide;

(E)-3-(dimethylamino)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)prop-1-ene-1-sulfonamide;

sodium (E)-((3-(dimethylamino)-3-methylbut-1-en-1-yl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

(S,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

- 5 (R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

or pharmaceutically acceptable salts of any of the compounds above.

- 10 Following is a list of abbreviations used in the description of the preparation of the compounds of the present invention:

μg: microgram

¹H NMR : Proton nuclear magnetic resonance

bs: broad singlet

- 15 CDCl₃: Deuterated chloroform

CHCl₃: Chloroform

d: doublet

DAMP: damage-associated molecular pattern;

DBU: 1,8-Diazabicyclo(5.4.0)undec-7-ene

- 20 DCM: Dichloromethane

dd: doublet of doublet

DMAC: N,N-(Dimethylacetamide)

DMAp: 4-(Dimethylamino) pyridine

DMF: N,N-Dimethyl formamide

- 25 DMSO: Dimethyl sulfoxide

dt: doublet of triplet

EDTA: Ethylenediaminetetraacetic acid

EtOAc: Ethyl acetate

EtOH: Ethanol

5 HCl(g): Hydrogen chloride (gas)

IL1 β : Interleukin 1 beta

K₂CO₃: Potassium carbonate

m: multiplet

MeOH: Methanol

10 mmol: millimoles

MS: Mass spectrum

N₂: Nitrogen

Na₂CO₃: Sodium carbonate

ng: nanogram

15 NIS: Nidosuccinimide

PAMP: pathogen-associated molecular pattern;

PMA: Phorbol 12-myristate 13-acetate

POCl₃: Phosphorylchloride

RM: reaction mixture

20 r.t., RT: room temperature

s: singlet

t: Triplet

td: triplet of doublet

THF: Tetrahydrofuran

25 TLC: Thin layer chromatography

TLR: Toll-like receptor.

TNF α : Tumor necrosis factor alpha

WT: Wild type

A441V: Alanine 441 position to Valine

E692K: Glutamic Acid 692 to Lysine

5 A439V: Alanine 439 position to Valine

A441V: Alanine 441 position to Valine

A439V: Alanine 439 position to Valine

The term “pharmaceutical composition” refers to a mixture of an NLRP3 antagonist or other compound described herein with other chemical components (referred to collectively
10 herein as “excipients”), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the NLRP3 antagonist or other compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to rectal, oral, and intravenous, aerosol, and parenteral, ophthalmic, pulmonary, and topical administration.

15 In an embodiment, the present invention provides effective amount of compound of formula (I) or its pharmaceutically acceptable salts may be selected from 1 mg to 500 mg; preferably 1 mg to 250 mg and more preferably 1 mg to 150 mg for the treatment and prevention of Cryopyrin Associated Periodic Syndromes (CAPS).

In certain other embodiments, the compound is administered orally in an amount to provide
20 compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 50 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 100 mg on each day the compound is administered to the subject. In certain embodiments,
25 the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 150 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a

pharmaceutically acceptable salt thereof in the range of about 1 mg to about 200 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 250 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 300 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 350 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 400 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 450 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 500 mg on each day the compound is administered to the subject.

In an embodiment, the present invention provides effective amount of compound of formula (I) or its pharmaceutically acceptable salt may be administered by oral, topical, parenteral, intravenous or intramuscular route of administration. In a preferred embodiment, the present invention provides effective amount of formula (I) or its pharmaceutically acceptable salts is administered by oral route of administration.

The compound of formula (I) or its pharmaceutically acceptable salts may be provided to the subject daily, weekly, as prescribed by physician to the person in need thereof.

In another embodiment, the present invention provides a method of treating a subject suffering from Cryopyrin Associated Periodic Syndromes (CAPS), which comprises

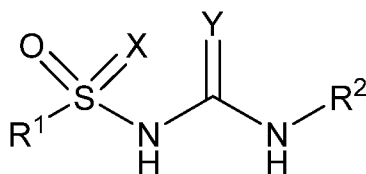
treatment of a patient in need of such therapy, with compound of formula (I) or its pharmaceutically acceptable salts or suitable pharmaceutical compositions containing them.

In an embodiment, the present invention provides the combination of compound of formula (I) and their pharmaceutically acceptable salts with other suitable agents as therapeutic agent for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In an embodiment, the additional therapeutic agent used is selected from Inhibitors of interleukin-1 β (e.g. Rilonacept, Canakinumab, and Anakinra); immune-suppressants (e.g., Methotrexate, Mercaptopurine, Cyclophosphamide), metabolic disorders drugs, glucocorticoids, non-steroidal anti-inflammatory drugs, Gasdermin D inhibitors (e.g., Necrosulfonamide); Cox-2 specific inhibitors, TNF- α binding proteins (e.g., Infliximab, Etanercept), Interferon-13, Interferon, Interleukin-2, antihistamines, beta-agonist, BTK inhibitors, anticholinergics, anti-cancer agents; anti-viral drugs, for example: Remdesivir, Lopinavir/Ritonavir, Favipiravir, Molnupiravir, Tamiflu; anti-malarial agents, for example: Chloroquine, Hydroxyl Chloroquine; or their suitable pharmaceutically acceptable salts. Further examples for use in combination with Non-Alcoholic Steato- Hepatitis (NASH) and fibrosis drugs; anticancer; antibiotics, for example Azithromycin; hormones, Aromatase inhibitors, Colchicine, Anticoagulants, antibodies, cytokines, anti-IL6 drugs; Antiparasitics; vaccines; Interferons; drug conjugates; Drugs originally developed for SARS (ACE2 protein decoy); Intravenous vitamin C; inhibitors of mitogen-activated protein kinase signaling (ex: BAY 43-9006); Syk inhibitors; mTOR inhibitors; antibodies (Rituxan); and BCR/ABL antagonist.

In yet another embodiment, compound of formula (I) is provided in the form of pharmaceutical composition.

In an embodiment, present invention provides a pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts for treatment of Cryopyrin Associated Periodic Syndromes (CAPS) wherein compound of formula (I) is



Formula (I)

In an embodiment, the present invention provides pharmaceutical composition comprising compound of formula (I) and suitable pharmaceutically acceptable excipients for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

The pharmaceutically acceptable excipients may be selected at least one from diluents, carriers, binders, disintegrating agents, lubricating agents, surface active agents and the like.

In an embodiment, the present invention provides a pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts wherein effective amount of compound of formula (I) or its pharmaceutically acceptable salt may be selected from 1 mg to 500 mg; preferably 1 mg to 250 mg and more preferably 1 mg to 150 mg for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In an embodiment, the present invention provides pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salt may be administered by oral, topical, parenteral, intravenous or intramuscular route of administration. In a preferred embodiment, the pharmaceutical composition may be administered by oral route of administration.

In another embodiment of the present invention provides a process for the preparation of a stable pharmaceutical composition of compounds of formula (1).

The stable pharmaceutical composition may be made by dry mixing, wet granulation or dry granulation methods by techniques known to persons skilled in the art. Thus, for example,

In wet granulation process, the drug is mixed with one or more pharmaceutical excipients and granulated with suitable binding solution as described earlier, to form wet granules, the wet granules are dried and optionally sieved. The dried granules are mixed with one or more suitable excipients from those described elsewhere and then compressed into tablets or filled into capsules.

In dry mixing process, the drug is mixed with all the pharmaceutical excipients required. The blend is mixed with one or more suitable excipients from those described elsewhere and then final blend is either compressed into tablets or filled in capsules.

In dry granulation process, the drug is mixed with one or more pharmaceutical excipients and compressed into slugs and these slugs are passed through required sieve. The sieved granules are mixed with one or more suitable excipients from those described elsewhere and then compressed into tablets or filled into capsules.

One or more solvents or vehicle used in the formulation are selected from water, acetone, chloroform, dichloromethane, ethyl alcohol, ethyl acetate, methyl alcohol, isopropyl alcohol and combinations thereof and other such materials known to those of ordinary skill in the art.

In yet another embodiment, the present invention provides the administration of compound of formula (I) and their pharmaceutically acceptable salts alone or in combination with other suitable agents as therapeutic agent for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In an embodiment, the additional therapeutic agent used is selected from Inhibitors of interleukin-1 β (e.g. Rilonacept, Canakinumab, and Anakinra); immune-suppressants (e.g., Methotrexate, Mercaptopurine, Cyclophosphamide), metabolic disorders drugs, glucocorticoids, non-steroidal anti-inflammatory drugs, Gasdermin D inhibitors (e.g., Necrosulfonamide); Cox-2 specific inhibitors, TNF- α binding proteins (e.g., Infliximab, Etanercept), Interferon-13, Interferon, Interleukin-2, antihistamines, beta-agonist, BTK inhibitors, anticholinergics, anti-cancer agents; anti-viral drugs, for example: Remdesivir,

Lopinavir/Ritonavir, Favipiravir, Molnupiravir, Tamiflu; anti-malarial agents, for example: Chloroquinone, Hydroxyl Chloroquinone; or their suitable pharmaceutically acceptable salts. Further examples for use in combination with Non-Alcoholic Steato- Hepatitis (NASH) and fibrosis drugs; anticancer; antibiotics, for example Azithromycin; hormones, Aromatase inhibitors, Colchicine, Anticoagulants, antibodies, cytokines, anti-IL6 drugs; Antiparasitics; vaccines; Interferons; drug conjugates; Drugs originally developed for SARS (ACE2 protein decoy); Intravenous vitamin C; inhibitors of mitogen-activated protein kinase signaling (ex: BAY 43-9006); Syk inhibitors; mTOR inhibitors; antibodies (Rituxan); and BCR/ABL antagonist.

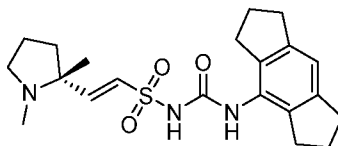
- 10 Compositions of the invention are also used in combination with other active ingredients. For the treatment of Arenaviridae virus infections, preferably, the other active therapeutic agent is active against Arenaviridae virus infections, particularly Lassa virus and Junin virus infections. Non-limiting examples of these other active therapeutic agents are Ribavirin, Favipiravir (also known as T-705 or Avigan), T-705 monophosphate, T-705 diphosphate, T-705 triphosphate, ST- 193, and mixtures thereof. T

- The compounds and compositions of the present invention are also intended for use with general care provided patients with Arenaviridae viral infections, including parenteral fluids (including dextrose saline and Ringer's lactate) and nutrition, antibiotic (including Metronidazole and Cephalosporin antibiotics, such as Ceftriaxone and Cefuroxime) and/or antifungal prophylaxis, fever and pain medication, antiemetic (such as Metoclopramide) and/or antidiarrheal agents, vitamin and mineral supplements (including Vitamin C or/and K and zinc sulfate), anti-inflammatory agents (such as Ibuprofen), pain medications, and medications for other common diseases in the patient population, such anti-malarial agents (including Artemether and Artesunate-lumefantrine combination therapy), typhoid (including quinolone antibiotics, such as Ciprofloxacin, macrolide antibiotics, such as Azithromycin, cephalosporin antibiotics, such as Ceftriaxone, or aminopenicillins, such as Ampicillin), or shigellosis.

The present invention further discloses use of said compound of formula (I) or their suitable pharmaceutical compositions for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In another embodiment, the present invention provides a method of treating Cryopyrin Associated Periodic Syndromes (CAPS) using pharmaceutical composition of compound of formula (I) or its pharmaceutically acceptable salts. In a preferred embodiment, a method of treating Cryopyrin Associated Periodic Syndromes (CAPS) using compound of formula (I) or its pharmaceutical composition.

In a preferred embodiment, the present invention provides compound of formula (11) or its pharmaceutically acceptable salts suitable for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).



Formula (11)

In a further preferred embodiment the present invention provides use of the compound of formula (11) or their suitable pharmaceutical compositions for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

The method comprises administering to a subject an effective amount of a compound according to Formula (11),

In another preferred embodiment, the present invention provides effective amount of compound of formula (11) or its pharmaceutically acceptable salt may be selected from 1 mg to 500 mg; preferably 1 mg to 250 mg and more preferably 1 mg to 150 mg for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In certain other embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 50 mg on each day the compound is administered to the subject. In

certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 100 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide
5 compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 150 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 200 mg on each day the compound is administered to the subject. In
10 certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 250 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of
15 about 1 mg to about 300 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 350 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide
20 compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 400 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 450 mg on each day the compound is administered to the subject. In
25 certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 500 mg on each day the compound is administered to the subject.

In another preferred embodiment, the present invention provides effective amount of compound of formula (11) or its pharmaceutically acceptable salt may be administered by
30 oral, topical, parenteral, intravenous or intramuscular route of administration. In a preferred

embodiment, the present invention provides effective amount of formula (11) or its pharmaceutically acceptable salt is administered by oral route of administration.

The compound of formula (11) or its pharmaceutically acceptable salts may be provided to the subject daily, weekly, as prescribed by physician to the person in need thereof.

- 5 In one of the preferred embodiment, the present invention provides the combination of compound of formula (11) and their pharmaceutically acceptable salts with other suitable agents as therapeutic agent for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

Wherein other suitable therapeutic agents may be selected from Inhibitors of interleukin-1 β (e.g. Rilonacept, Canakinumab, and Anakinra); immune-suppressants (e.g., Methotrexate, Mercaptopurine, Cyclophosphamide), metabolic disorders drugs, glucocorticoids, non-steroidal anti-inflammatory drugs, Gasdermin D inhibitors (e.g., Necrosulfonamide); Cox-2 specific inhibitors, TNF- α binding proteins (e.g., Infliximab, Etanercept), Interferon-13, Interferon, Interleukin-2, antihistamines, beta-agonist, BTK inhibitors, anticholinergics, anti-cancer agents; anti-viral drugs, for example: Remdesivir, Lopinavir/Ritonavir, Favipiravir, Molnupiravir, Tamiflu; anti-malarial agents, for example: Chloroquine, Hydroxyl Chloroquine; or their suitable pharmaceutically acceptable salts. Further examples for use in combination with Non-Alcoholic Steato- Hepatitis (NASH) and fibrosis drugs; anticancer; antibiotics, for example Azithromycin; hormones, Aromatase inhibitors, Colchicine, Anticoagulants, antibodies, cytokines, anti-IL6 drugs; Antiparasitics; vaccines; Interferons; drug conjugates; Drugs originally developed for SARS (ACE2 protein decoy); Intravenous vitamin C; inhibitors of mitogen-activated protein kinase signaling (ex: BAY 43-9006); Syk inhibitors; mTOR inhibitors; antibodies (Rituxan); and BCR/ABL antagonist may also be used in combination with compound of formula (11) for treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In a preferred embodiment, present invention provides a pharmaceutical composition comprising compound of formula (11) or its pharmaceutically acceptable salts for treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In another preferred embodiment, the present invention provides pharmaceutical composition comprising compound of formula (11) and suitable pharmaceutically acceptable excipients for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

- 5 The pharmaceutically acceptable excipients may be selected at least one from diluents, carriers, binders, disintegrating agents, lubricating agents, surface active agents and the like.

In another preferred embodiment, the present invention provides the pharmaceutical composition comprising compound of formula (11), its pharmaceutically acceptable salts
10 and optionally other suitable therapeutic agents for treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

Wherein other suitable therapeutic agents may be selected from Inhibitors of interleukin-1 β (e.g. Rilonacept, Canakinumab, and Anakinra); immune-suppressants (e.g., Methotrexate, Mercaptopurine, Cyclophosphamide), metabolic disorders drugs, glucocorticoids, non-steroidal anti-inflammatory drugs, Gasdermin D inhibitors (e.g., Necrosulfonamide); Cox-2
15 specific inhibitors, TNF- α binding proteins (e.g., Infliximab, Etanercept), Interferon-13, Interferon, Interleukin-2, antihistamines, beta-agonist, BTK inhibitors, anticholinergics, anti-cancer agents; anti-viral drugs, for example: Remdesivir, Lopinavir/Ritonavir, Favipiravir, Molnupiravir, Tamiflu; anti-malarial agents, for example: Chloroquinone, Hydroxyl
20 Chloroquinone; or their suitable pharmaceutically acceptable salts. Further examples for use in combination with Non-Alcoholic Steato-Hepatitis (NASH) and fibrosis drugs; anticancer; antibiotics, for example Azithromycin; hormones, Aromatase inhibitors, Colchicine, Anticoagulants, antibodies, cytokines, anti-IL6 drugs; Antiparasitics; vaccines; Interferons; drug conjugates; Drugs originally developed for SARS (ACE2 protein decoy);
25 Intravenous vitamin C; inhibitors of mitogen-activated protein kinase signaling (ex: BAY 43-9006); Syk inhibitors; mTOR inhibitors; antibodies (Rituxan); and BCR/ABL antagonist may also be used in combination with compound of formula (11) for treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In an embodiment, the present invention provides a pharmaceutical composition comprising compound of formula (11) or its pharmaceutically acceptable salts wherein effective amount of compound of formula (11) or its pharmaceutically acceptable salt may be selected from 1 mg to 500 mg; preferably 1 mg to 250 mg and more preferably 1 mg to 150 mg for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In another embodiment, the present invention further discloses use of said compound of formula (11) or their suitable pharmaceutical compositions for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

In another embodiment, the present invention provides use of the compound of formula (11) wherein the compound is administrated in a daily dosage range is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

In another preferred embodiment, the present invention provides a method of treating Cryopyrin Associated Periodic Syndromes (CAPS) using pharmaceutical composition of compound of formula (11) or its pharmaceutically acceptable salts. In a preferred embodiment, a method of treating Cryopyrin Associated Periodic Syndromes (CAPS) using compound of formula (11) or its pharmaceutical composition.

In another preferred embodiment of the present invention provides a process for the preparation of a stable pharmaceutical composition of compounds of formula (11).

The stable pharmaceutical composition may be made by dry mixing, wet granulation or dry granulation methods by techniques known to persons skilled in the art. Thus, for example,

In wet granulation process, the drug is mixed with one or more pharmaceutical excipients and granulated with suitable binding solution as described earlier, to form wet granules, the wet granules are dried and optionally sieved. The dried granules are mixed with one or more suitable excipients from those described elsewhere and then compressed into tablets or filled into capsules.

In dry mixing process, the drug is mixed with all the pharmaceutical excipients required. The blend is mixed with one or more suitable excipients from those described elsewhere and then final blend is either compressed into tablets or filled in capsules.

5 In dry granulation process, the drug is mixed with one or more pharmaceutical excipients and compressed into slugs and these slugs are passed through required sieve. The sieved granules are mixed with one or more suitable excipients from those described elsewhere and then compressed into tablets or filled into capsules.

10 One or more solvents or vehicle used in the formulation are selected from water, acetone, chloroform, dichloromethane, ethyl alcohol, ethyl acetate, methyl alcohol, isopropyl alcohol and combinations thereof and other such materials known to those of ordinary skill in the art.

In an embodiment, the pharmaceutically acceptable excipients described in the present invention are selected at least one from diluents, carriers, binders, disintegrating agents, lubricating agents, surface active agents and the like.

15 Diluents include, but are not limited to lactose monohydrate, polymethacrylates selected from Eudragit, potassium chloride, sulfobutylether β -cyclodextrin, sodium chloride and spray dried lactose, combinations thereof and other such materials known to those of ordinary skill in the art.

20 Carriers include, but are not limited to lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate and kaolin, crystalline cellulose and silicic acid, combinations thereof and other such materials known to those of ordinary skill in the art.

25 Binders include, but are not limited to carbomers selected from carbopol, gellan, gum Arabic, hydrogenated vegetable oil, polymethacrylates selected from Eudragit, xanthan, lactose and Zein, combinations thereof and other such materials known to those of ordinary skill in the art.

Disintegrating agents include, but are not limited to, bicarbonate salt, chitin, gellan gum, polacrillin potassium and docusate sodium, combinations thereof and other such materials known to those of ordinary skill in the art.

5 Lubricating agents used include, but are not limited to, glycerin behenate, hydrogenated vegetable oil, sodium stearyl fumarate and myristic acid, combinations thereof and other such materials known to those of ordinary skill in the art.

Surface active agents include but are not limited to, nonionic surfactant selected from alkyl polyglucosides, cocamide DEA, cocamide MBA, cocamide TEA, decyl maltoside and octyl glucoside; anionic surfactant selected from arachnidan acid and arachidonic acid;
10 cationic surfactant selected from cetyl trimethylammonium bromide and cetylpyridinium chloride, combinations thereof and other such materials known to those of ordinary skill in the art.

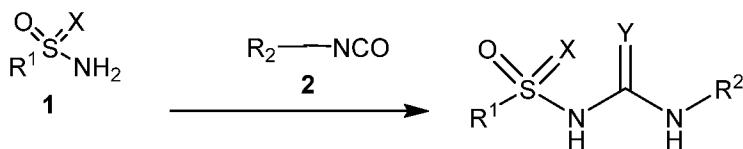
General Process for Preparation

The novel compounds of the present invention can be prepared using the reactions and
15 techniques described below, together with conventional techniques known to those skilled in the art of organic synthesis, or variations thereon as appreciated by those skilled in the art.

The reactions can be performed in solvents appropriate to the reagents and materials employed and suitable for the transformations being affected. Preferred methods include,
20 but not limited to those described below, where all symbols are as defined earlier unless and otherwise defined below.

The compounds of the general formula (I) can be prepared as described in schemes below along with suitable modifications/variations which are well within the scope of a person skilled in the art.

25 Scheme 1



Formula (I)

Wherein each of R^1 , R^2 , X, and Y, are as defined earlier. Compound **1** and Compound **2** can be prepared by variety of methods familiar to those skilled in art using reported procedures.

- 5 Compound (**1**) on treatment with isocyanato derivative (**2**) under suitable conditions in presence of base like sodium hydride and appropriate solvent to afford compound of formula (**I**).

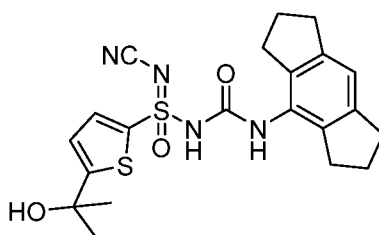
Specific reaction conditions, solvents and other parameters necessary for carrying out the process steps as described above are well within the capabilities of a person skilled in the art.

The invention is further illustrated by the following non-limiting examples which describe the preferred way of carrying out the present invention. These are provided without limiting the scope of the present invention in any way.

- ^1H NMR spectral data given in the examples (vide infra) are recorded using a 400 MHz spectrometer (Bruker AVANCE-400) and reported in δ scale. Until and otherwise mentioned the solvent used for NMR is CDCl_3 using TMS as the internal standard.

Example – 1

N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide

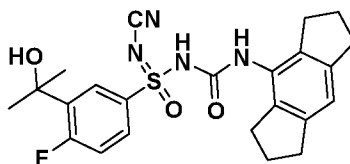


^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 7.95 (bs, 1H), 7.23 (d, J = 4.0 Hz, 1H), 6.82 (d, J = 4.0 Hz, 1H), 6.81 (s, 1H), 5.63 (s, 2H), 2.77 (t, J = 7.2 Hz, 4H), 2.68 – 2.65 (m, 4H), 1.94 (qui, J = 7.2 Hz, 4H), 1.49 (s, 6H); MS (ESI): m/z (%) = 445.10 (100%) ($\text{M}+\text{H}$) $^+$, 443.10 (100%) ($\text{M}-\text{H}$).

5

Example 2

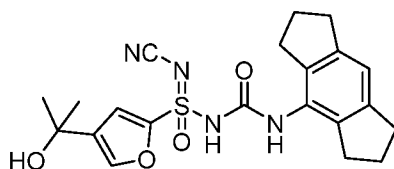
N'-cyano-4-fluoro-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide



^1H NMR (400 MHz, DMSO): δ = 8.13 (dd, J =2.4Hz, J =7.6Hz, 1H), 8.00 (bs, 1H), 7.68-7.64 (m, 1H), 7.24-7.19 (m, 2H), 6.79 (s, 1H), 2.76-2.60 (m, 8H), 1.95-1.85 (m, 4H), 1.50 (s, 3H), 1.48 (s, 3H); MS (ESI): m/z (%) = 456.88 (100%) ($\text{M}+\text{H}$) $^+$.

Example – 3

N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide



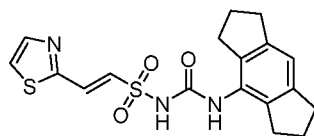
15

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 8.10 (bs, 1H), 7.55 (s, 1H), 6.82 (s, 1H), 6.79 (s, 1H), 5.03 (s, 1H), 2.77 (t, J = 7.2 Hz, 4H), 2.68 (t, J = 7.2 Hz, 4H), 1.94 (qui, J = 7.2 Hz, 4H), 1.38 (s, 6H); MS (ESI): m/z (%) = 429.20 (100%) ($\text{M}+\text{H}$) $^+$, 427.30 (100%) ($\text{M}-\text{H}$).

Example 4

20

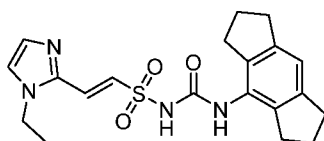
(E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(thiazol-2-yl)ethenesulfonamide



¹H NMR (400 MHz, DMSO-*d*₆, D₂O-*X*): δ = 10.7 (br, s, 1H), 8.23 (s, 1H), 8.05 (d, *J* = 2.8 Hz, 1H), 8.02 (d, *J* = 2.8 Hz, 1H), 7.74 (d, *J* = 15.2 Hz, 1H), 7.58 (d, *J* = 15.2 Hz, 1H), 6.96 (s, 1H), 2.79 (t, *J* = 7.2 Hz, 4H), 2.66 (t, *J* = 6.8 Hz, 4H), 1.98 – 1.91 (m, 4H); MS (ESI): *m/z* (%) = 389.92 (100%) (M+H)⁺, 411.90 (20%) (M+Na)⁺.

Example 5

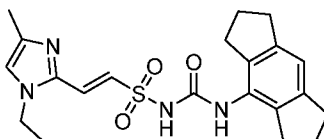
(E)-2-(1-ethyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide



¹H NMR (400 MHz, DMSO): δ = 10.55 (bs, 1H), 8.20 (s, 1H), 7.46-7.42 (m, 2H), 7.29 (d, *J*=14.8Hz, 1H), 7.13 (s, 1H), 6.95 (s, 1H), 4.16 (q, *J*=7.2Hz, 2H), 2.82-2.78 (m, 4H), 2.67-2.64 (m, 4H), 1.98-1.91 (m, 4H), 4.16 (t, *J*=7.2Hz, 3H); MS (ESI): *m/z* (%) = 401.15 (100%) (M+H)⁺; 423.15 (50%) (M+Na)⁺.

Example 6

(E)-2-(1-ethyl-4-methyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide

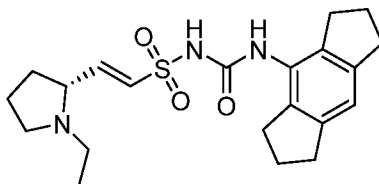


^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 10.55 (s, 1H), 8.16 (s, 1H), 7.36 (d, J = 14.8 Hz, 1H), 7.21 (d, J = 14.8 Hz, 1H), 7.17 (s, 1H), 6.95 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 4H), 2.66 (t, J = 7.2 Hz, 4H), 2.12 (s, 3H), 1.98 – 1.91 (m, 4H), 1.27 (d, J = 7.2 Hz, 3H); MS (ESI): m/z (%) = 415.18 (100%) ($\text{M}+\text{H}$) $^+$.

5

Example-7

(R,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide



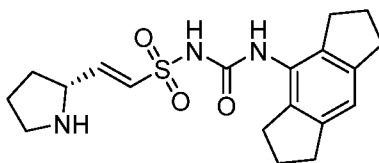
10

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 8.03 (s, 1H), 6.92 (s, 1H), 6.87 (d, J =14.8Hz, 1H), 6.60-6.54 (m, 1H), 3.27-3.16 (m, 3H), 2.80 (t, J =7.2Hz, 4H), 2.67 (t, J =7.2Hz, 4H), 2.35-2.33 (m, 2H), 2.09-1.94 (m, 6H), 1.81-1.73 (m, 2H), 1.03 (t, J =7.2Hz, 3H); MS (ESI): m/z (%) = 404.20 (100%) ($\text{M}+\text{H}$) $^+$.

Example-8

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(pyrrolidin-2-yl)ethene-1-sulfonamide

15

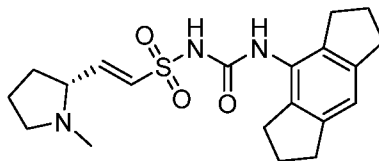


20

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 9.71 (brs, 1H), 7.49 (s, 1H), 6.95 (d, J = 15.2 Hz, 1H), 6.80 (s, 1H), 6.36 (dd, J = 7.2 Hz, J = 15.2 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.18 – 3.03 (m, 2H), 2.77 (t, J = 7.2 Hz, 4H), 2.70 (t, J = 7.2 Hz, 4H), 2.14 – 2.07 (m, 4H), 2.03 – 1.80 (m, 6H), 1.70 – 1.60 (m, 1H); MS (ESI): m/z (%) = 376.10 (100%) ($\text{M}+\text{H}$) $^+$, 374.05 (100%) ($\text{M}-1$).

Example-9

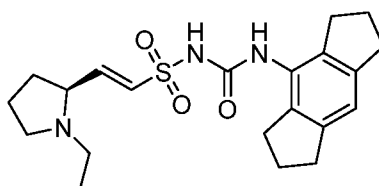
(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-methylpyrrolidin-2-yl)ethene-1-sulfonamide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.53 (brs, 1H), 7.97 (s, 1H), 6.92 (s, 1H), 6.84 (d, *J* = 15.2 Hz, 1H), 6.53 (dd, *J* = 7.6 Hz, *J* = 15.2 Hz, 1H), 3.13 – 3.04 (m, 1H), 3.05 – 2.92 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 4H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.33 – 2.28 (m, 1H), 2.26 (s, 3H), 2.05 – 1.91 (m, 5H), 1.79 – 1.72 (m, 2H), 1.59 – 1.54 (m, 1H); MS (ESI): *m/z* (%) = 390.17 (100%) (M+H)⁺, 388.07 (30%) (M-1).

Example-10

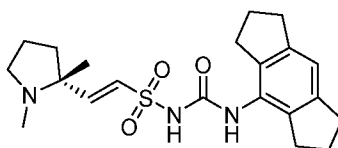
(S,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethanesulfonamide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.03 (s, 1H), 6.92 (s, 1H), 6.87 (d, *J*=14.8Hz, 1H), 6.60-6.54 (m, 1H), 3.27-3.16 (m, 3H), 2.80 (t, *J*=7.2Hz, 4H), 2.67 (t, *J*=7.2Hz, 4H), 2.35-2.33 (m, 2H), 2.09-1.94 (m, 6H), 1.81-1.73 (m, 2H), 1.03 (t, *J*=7.2Hz, 3H); MS (ESI): *m/z* (%) = 404.20 (100%) (M+H)⁺.

Example-11

(R,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide

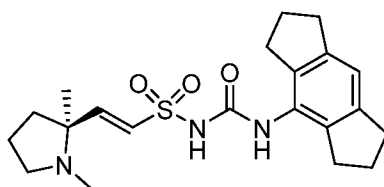


^1H NMR (400 MHz, DMSO- d_6): δ = 8.04 (s, 1H), 6.93 (s, 1H), 6.74 (d, J = 15.6 Hz, 1H), 6.65 (d, J = 15.2 Hz, 1H), 2.93 – 2.86 (m, 1H), 2.80 (t, J = 7.2 Hz, 4H), 2.67 (t, J = 7.2 Hz, 4H), 2.19 (s, 3H), 1.99 – 1.91 (m, 5H), 1.80 – 1.69 (m, 4H), 1.13 (s, 3H), MS (ESI): m/z (%) = 404.16 (100%) ($\text{M}+\text{H}$) $^+$.

5

Example-12

(S,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide

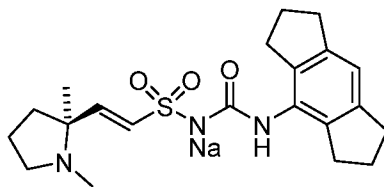


^1H NMR (400 MHz, DMSO- d_6): δ = 8.04 (s, 1H), 6.93 (s, 1H), 6.73 (d, J = 15.2 Hz, 1H), 6.65 (d, J = 15.2 Hz, 1H), 2.80 (t, J = 7.2 Hz, 4H), 2.68 (t, J = 7.2 Hz, 4H), 2.20 (s, 3H), 1.96 (m, 4H), 1.72 (m, 4H), 1.13 (s, 3H); MS (ESI): m/z (%) = 404.25 (100%) ($\text{M}+1$).

10

Example-13

sodium(S,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide



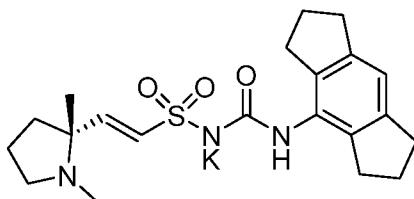
15

^1H NMR (400 MHz, DMSO- d_6): δ = 7.33 (s, 1H), 6.77 (s, 1H), 6.56 (d, J = 15.2 Hz, 1H), 6.16 (d, J = 16 Hz, 1H), 2.76 (t, J = 7.2 Hz, 4H), 2.69 (t, J = 7.2 Hz, 4H), 2.62 (m, 1H), 2.08 (s, 3H), 1.90 (m, 4H), 1.72 (m, 4H), 1.60 (m, 3H), 1.01 (s, 3H); MS (ESI): m/z (%) = 404.20 (100%) ($\text{M}+1$).

20

Example-14

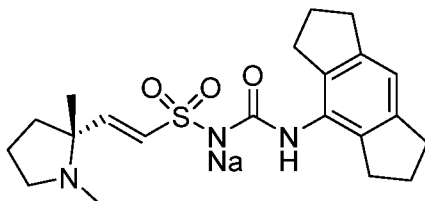
potassium (R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.33 (s, 1H), 6.77 (s, 1H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.18 (d, *J* = 15.6 Hz, 1H), 2.77 – 2.72 (m, 5H), 2.69 (t, *J* = 7.2 Hz, 4H), 2.64 – 2.58 (m, 1H), 2.08 (s, 3H), 1.90 (quin, *J* = 7.6 Hz, 4H), 1.75 – 1.70 (m, 3H), 1.62 – 1.60 (m, 1H), 1.01 (s, 3H); MS (ESI): *m/z* (%) = 404.21 (100%) (M-K)⁺.

Example-15

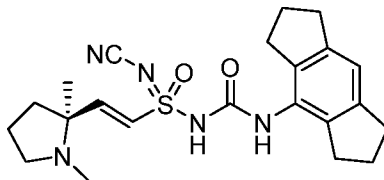
Sodium(R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.36 (s, 1H), 6.77 (s, 1H), 6.57 (d, *J* = 15.6 Hz, 1H), 6.19 (d, *J* = 15.6 Hz, 1H), 2.76 (t, *J* = 7.2 Hz, 5H), 2.69 (t, *J* = 7.2 Hz, 4H), 2.64 – 2.59 (m, 1H), 2.08 (s, 3H), 1.91 (quin, *J* = 7.6 Hz, 4H), 1.74 – 1.68 (m, 3H), 1.62 – 1.60 (m, 1H), 1.01 (s, 3H); MS (ESI): *m/z* (%) = 404.17 (100%) (M-Na)⁺.

Example-16

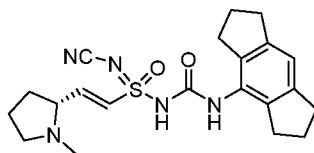
(E)-N'-cyano-2-((S)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.94 (s, 1H), 8.06 (s, 1H), 6.97 (d, *J* = 16.0 Hz, 1H), 6.83 (s, 1H), 6.56 – 6.48 (m, 1H), 3.58 (br s, 1H), 3.24 – 3.12 (m, 1H), 2.77 (t, *J* = 7.2 Hz, 4H), 2.69 (t, *J* = 7.2 Hz, 7H), 2.10 – 1.99 (m, 3H), 1.95 – 1.88 (m, 5H), 1.53 – 1.36 (m, 3H); ESI-Q-TOF-MS: *m/z* [M-HCl+H]⁺ calcd for [C₂₂H₃₀N₅O₂S]⁺: 428.2120; found: 428.2052

Example-17

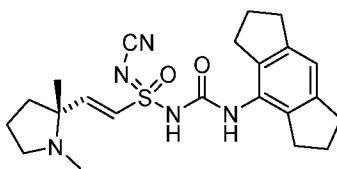
(E)-N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-((R)-1-methylpyrrolidin-2-yl)ethene-1-sulfonimidamide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.82 (s, 1H), 8.06 (s, 1H), 7.11 – 7.02 (m, 1H), 6.83 (s, 1H), 6.43 – 6.35 (m, 1H), 4.99 (br s, 1H), 3.62 – 3.61 (m, 1H), 3.09 – 3.07 (m, 1H), 2.77 (t, *J* = 7.2 Hz, 7H), 2.70 (t, *J* = 7.2 Hz, 4H), 2.33 – 2.27 (m, 1H), 2.1 – 1.88 (m, 7H); MS (TOF): *m/z* (%) = 414.1897 (100%) (M+H)⁺, 412.1765 (100%) (M-1)⁻.

Example-18

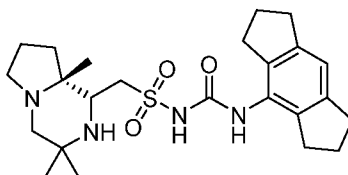
(E)-N'-cyano-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.98 (s, 1H), 8.03 (s, 1H), 6.94 – 6.90 (m, 1H), 6.83 (s, 1H), 6.54 – 6.51 (m, 1H), 2.77 (t, *J* = 7.2 Hz, 5H), 2.70 (t, *J* = 7.2 Hz, 5H), 2.62 (br s, 3H), 1.99 – 1.90 (br s, 2H), 1.97 – 1.93 (m, 6H), 1.48 – 1.46 (m, 3H); MS (TOF): *m/z* (%) = 428.2097 (100%) (M+H)⁺, 426.1941 (60%) (M-1)⁻.

Example-19

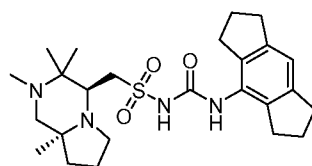
N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((1S,8aR)-3,3,8a-trimethyloctahydropyrrolo[1,2-a]pyrazin-1-yl)methanesulfonamide



¹H NMR (400 MHz, DMSO-d₆): δ = 7.92 (s, 1H), 6.87 (s, 1H), 3.42 - 3.26 (m, 5H), 3.07 - 3.01 (m, 1H), 2.89 - 2.80 (m, 1H), 2.89 - 2.80 (m, 1H), 2.77 (t, *J*=7.2Hz, 4H), 2.73 - 2.67 (m, 4H), 2.58 - 2.44 (m, 1H), 2.38 - 2.33 (m, 1H), 1.98 - 1.92 (m, 4H), 1.69 - 1.61 (m, 2H), 1.31 (s, 3H), 1.18 (s, 3H), 0.78 (s, 3H); MS (TOF): *m/z* (%) = 461.2537 (100%) (M+H)⁺.

Example-20

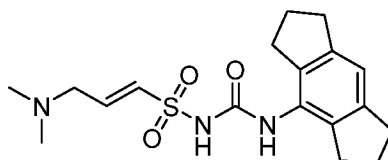
N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((4S,8aS)-2,3,3,8a-tetramethyloctahydropyrrolo[1,2-a]pyrazin-4-yl)methanesulfonamide



¹H NMR (400 MHz, DMSO-d₆): δ = 8.03 (s, 1H), 6.93 (s, 1H), 3.52 - 3.48 (m, 2H), 3.18 - 3.09 (m, 1H), 3.09 - 3.01 (m, 1H), 3.00 - 2.88 (m, 1H), 2.81 (t, *J* = 7.2 Hz, 4H), 2.70 (t, *J* = 7.2 Hz, 4H), 2.36 - 2.33 (m, 2H), 2.19 (s, 3H), 2.01 - 1.93 (m, 4H), 1.76 - 1.69 (m, 1H), 1.67 - 1.54 (m, 3H), 1.01 - 1.04 (m, 6H), 0.86 (s, 3H); MS (TOF): *m/z* (%) = 475.2709 (100%) (M+H)⁺, 473.2593 (20%) (M-1).

Example-21

(E)-3-(dimethylamino)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)prop-1-ene-1-sulfonamide

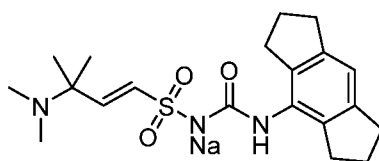


¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.22 (brs, 1H), 7.94 (s, 1H), 6.91 (s, 1H), 6.86 (d, *J* = 15.2 Hz, 1H), 6.62 – 6.55 (m, 1H), 3.27 (t, *J* = 6.0 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 4H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.30 (s, 6H), 1.99 – 1.91 (m, 4H); **MS (ESI):** *m/z* (%) = 364.1513 (100%) (M+H)⁺.

5

Example-22

sodium (E)-((3-(dimethylamino)-3-methylbut-1-en-1-yl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide

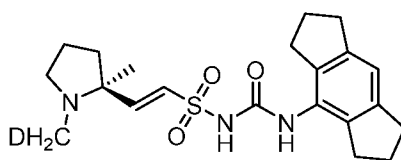


¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.36 (s, 1H), 6.77 (s, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 2.76 (t, *J* = 7.2 Hz, 4H), 2.69 (t, *J* = 7.2 Hz, 4H), 2.11 (s, 1H), 1.94 – 1.87 (m, 4H), 1.06 (s, 6H); **MS (TOF):** *m/z* (%) = 392.1987 (100%) (M+H)⁺, 390.1841 (20%) (M-1).

15

Example-23

(S,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide

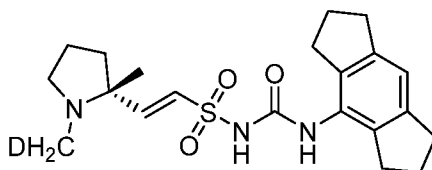


¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.93 (s, 1H), 6.91 (s, 1H), 6.71 (d, *J* = 15.2 Hz, 1H), 6.60 (d, *J* = 15.6 Hz, 1H), 2.85 – 2.83 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 4H), 2.73 – 2.71 (m, 1H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.15 (s, 2H), 1.95 (quin, *J* = 7.2 Hz, 4H), 1.81 – 1.69 (m, 4H), 1.10 (s, 3H). **ESI-Q-TOF-MS:** *m/z* 405.2268 (100%) [M+H]⁺, 403.1901 (100%) [M-H]⁻.

20

Example-24

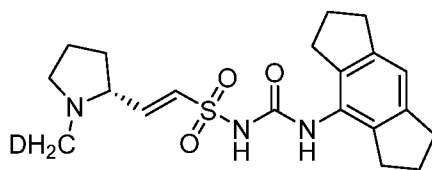
(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.94 (s, 1H), 6.91 (s, 1H), 6.72 (d, *J* = 15.2 Hz, 1H), 6.61 (d, *J* = 15.2 Hz, 1H), 2.88 – 2.83 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 4H), 2.75 – 2.71 (m, 1H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.15 (s, 2H), 1.95 (quin, *J* = 7.2 Hz, 4H), 1.82 – 1.69 (m, 4H), 1.11 (s, 3H), ESI-Q-TOF-MS: *m/z* 405.2104 (100%) [M+H]⁺, 403.1915 (100%) [M-H][−].

Example-25

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide



¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.5 (br s, 1H), 7.99 (s, 1H), 6.92 (s, 1H), 6.86 (d, *J* = 15.2 Hz, 1H), 6.56 (dd, *J*₁ = 7.6 Hz, *J*₂ = 15.2 Hz, 1H), 3.12 – 3.06 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 4H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.38 – 2.32 (m, 1H), 2.25 (s, 2H), 2.08 – 2.01 (m, 1H), 1.95 (quin, *J* = 7.2 Hz, 4H), 1.80 – 1.73 (m, 2H), 1.63 – 1.54 (m, 1H), ESI-Q-TOF-MS: *m/z* 391.1956 (100%) [M+H]⁺, 389.1756 (100%) [M-H][−].

In vitro study to evaluate the potency in healthy volunteers and against CAPS mutations:

Compound 11, a potent NLRP3 inflammasome inhibitor blocks the IL-1 β and IL-18 secretion from activated THP-1 cells, hPBMCs (Human peripheral blood mononuclear cell) and whole blood treated with LPS (lipopolysaccharide) and ATP (Adenosine triphosphate).

For the whole blood assay, human peripheral venous blood was collected from healthy volunteers following the protocol approved by ethics committee. Whole blood was distributed in 96-well plates and primed with LPS (500ng/mL) for 4 hours. Different concentrations of compound 11 was added in the presence of serum free media. NLRP3 inflammasome was induced with ATP (5mM) for 1hour. The supernatant was collected at the end of 1 hour and assayed for released IL-1 β using the ELISA method. The inhibition in the cytokine levels was plotted and the half maximal inhibitory concentration was derived.

Table 1: Half maximal inhibitory concentration of Compound 11 against NLRP3 mediated IL-1 β release in PBMCs from healthy volunteers

Whole Blood assay (Normal volunteer)	IC ₅₀ (nM) Mean $\pm$ SD*
Compound 11	186 $\pm$ 32

* Mean data from three healthy volunteers

Ex-vivo pharmacodynamics evaluation

In the ex-vivo pharmacodynamics evaluation, the blood was withdrawn at specific intervals after dosing and NLRP3 was induced using LPS and ATP. Inhibition of IL-1 β secretion was observed over 90% with all the doses tested in SAD and MAD studies. An ED₉₀ was achieved below 400ng/mL.

To examine the efficacy of Compound 11 in CAPS condition, initially the potency of Compound 11 was tested against different CAPS mutations. Human PBMCs containing monocytes express NLRP3 when induced with LPS and ATP in normal volunteers or only with LPS in CAPS patient volunteers. Human peripheral blood mononuclear cell (hPBMC) was isolated from volunteer using gradient method. hPBMC was suspended in complete growth medium and plated overnight before activating with LPS and/or ATP. Half maximal inhibitory concentrations were derived for Compound 11 against normal volunteer and CAPS patient PBMCs activated with respective stimulants and subsequent treatment with Compound 11. Compound 11 showed IC₅₀ of 3.0-6.0 nM in PBMCs isolated from healthy volunteers. When tested in 5 different CAPS patient volunteer PBMCs, Compound 11

showed potency between 2.2nM and 31.3nM. Interestingly the potency of Compound 11 was superior to the published report of MCC950, a competitor molecule where the potency was lower in similar family of mutations. Head to head in a A439V mutation, while Compound 11 was 15.1 and 31.3 nM, MCC950 showed $IC_{50} \geq 100nM$. (Wellcome Open Research 2020, 5:247)

Table 2: Half maximal inhibitory concentration of Compound 11 against NLRP3 mediated IL-1 β release in PBMCs from healthy and CAPS volunteers

Compound 11	Healthy Volunteers	CAPS patient Volunteers				
NLRP3 Mutation	WT (Wild Type)	A441V	E692K	A439V	A441V	A439V
IC ₅₀	3.0-6.0 nM*	2.7 nM	2.2nM	15.1nM	30.3nM	31.3nM

* PBMCs from normal volunteers (NLRP3 WT) were challenged with 10ng LPS and 5mM ATP to activate the inflammasome complex and secreted IL-1 β was measured. PBMCs from CAPS patient volunteers (NLRP3 mutant) were challenged with 100ng LPS to activate the inflammasome complex and secreted IL-1 β was measured.

In a phase 1 single ascending dose clinical study, Compound 11 showed a good pharmacokinetic profile with dose dependent modulation in the plasma levels of healthy volunteers. In the multiple ascending BID study too, Compound 11 achieved steady state levels dose dependently.

In conclusion, Compound 11 had shown nM potency in NLRP3 mediated IL-1 β inhibition in preclinical studies and studies involving human healthy patients with wild type NLRP3, also showed a perfect translation in the clinic. Interestingly, it turned out to be equally potent in NLRP3 mediated IL-1 β inhibition in proven CAPS patients with defined gain of function mutation of NLRP3

Efficacy of Compound 11 in healthy adult human subjects:

Protocol Title: A Phase 1, Prospective study of the compound 11 administered via oral route to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics in Healthy Adult Human Subjects.

Objectives:

5 **Primary Objective:**

- To evaluate safety and tolerability of the compound 11 administered to healthy subjects.

Secondary Objective(s):

- 10
- To characterize the pharmacokinetics of the compound 11 when administered as a single oral dose to healthy subjects.
 - To evaluate pharmacodynamic properties of the compound 11 in healthy subjects.

Exploratory(s):

- 15
- To profile and identify/quantify unique metabolite(s) of the compound 11 in plasma and urine.
 - To evaluate any other pharmacodynamic properties of the compound 11 in healthy subjects.

Criteria for Safety:

- 20
- Recording of vital signs like body temperature, blood pressure, Respiratory rate, SpO₂ and radial pulse.
 - Clinical examinations, which include general examination as well as systemic examination (cardiovascular system (CVS), respiratory system (RS), gastrointestinal system (GI), central nervous system (CNS))
 - ECG evaluation

25

 - Clinical laboratory tests(i.e. hematology, serum biochemistry, urinalysis, and serology)
 - Frequency and severity of adverse events (AEs) for all subjects enrolled are recorded. All AEs, are classified using
 - causality
 - severity

30

 - seriousness

Methodology:

35 It is an open label, study designed to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) following a single-oral dose administration of the compound 11 to healthy subjects.

In this study each cohort containing six subjects, given a single oral dose of the compound 11 in ascending manner. Initially, up to 3 cohorts (comprising of 25 mg, 50 mg and 100 mg dose) of 18 subjects will be enrolled and dosed. Interim analysis is done after completion of three cohorts and submitted to Central Licensing Authority.

- 5 • Duration of the treatment: single dose
- Subjects were eligible for inclusion into the study if they were healthy, aged 18 through 55 years (both inclusive), had a body mass index (BMI) between 18.5 and 30.0 kg/m² (both inclusive) with a body weight of 50 to 100 kg (both inclusive), had normal QTc interval [QTcF ≤ 450 ms] at screening and check-in, agreed to
10 comply with trial procedures and willing to practice highly effective contraception.
- Subjects were excluded from the study if they have history or presence of systemic disorders/disease within the past 3 months; history of clinically significant hypersensitivity, intolerance, or allergies; history of COVID-19
15 infection within 14 days or contact with a confirmed active COVID-19 positive patient within 14 days; or positive COVID-19 test within 5 days of check-in; subjects who had systolic blood pressure more than 140 mmHg or less than 100 mmHg or diastolic blood pressure more than 90 mmHg or less than 60 mmHg; Pulse rate less than 55/minute or more than 100/minute and other exclusion
20 criteria as defined in protocol.
- Such subjects are invited to participate in this study.
- Evaluation for safety and efficacy is done as per the activity chart.

No. of subjects in treatment arm: A total of 18 subjects i.e. 06 subject in each cohort S1
25 (25 mg), cohort S2 (50 mg) and cohort S3 (100 mg) were enrolled. A total of 18 subjects were enrolled and dosed with the compound capsule. A total of 17 subjects completed the study.

Duration of treatment: Subjects were enrolled within 28 day screening period, received single doses of the compound 11 capsule orally and followed up for upto 48 hours post
30 dose

Results –

Of 18 enrolled subjects, 17 subjects completed the study. All 18 subjects were Asian, Male subjects. Overall, for this study the mean (range) age was 37 years (23 to 47 years) and BMI was 23.51 kg/m² (19.71 to 28.01 kg/m²). The compound administered via oral route
35 was found to be safe and well tolerated till 100 mg single dose in healthy subjects. No subjects were discontinued from the study because of adverse events.

Pharmacokinetic and Pharmacokinetic Results

Pharmacokinetic Results

The plasma and urine samples were analyzed for estimation of the compound using a separately validated LC-MS/MS assays. The concentration-time data were subjected for evaluation of pharmacokinetic parameters.

Cohort S1 (25 mg dose)

A total 06 healthy male subjects received 25 mg dose of the compound 11.

Note: 01 subject in cohort S1 withdrawn his consent and discontinued from the study. Hence, this subject was not used for pharmacokinetic assessment.

- Pharmacokinetic evaluation indicated that the drug was well absorbed on oral administration, with median time to reach maximal plasma concentration, median T_{max} is at 1.500 hr ranging from 0.500 hrs to 2.000 hrs. The mean elimination half-life was 6.526 ± 0.67 hrs. The mean C_{max} and AUC_{0-t} were 3.393 ± 0.72 µg/mL and 26.967 ± 0.39 hr*µg/mL, respectively. The mean plasma clearance was 0.922 ± 0.01 L/hr and mean volume of distribution was 8681.147 ± 929.14 mL. Mean cumulative percentage urinary recovery of an unchanged the compound was 93.26%.

Cohort S2 (50 mg dose)

A total 06 healthy male subjects received 50 mg dose of the compound 11.

- Pharmacokinetic evaluation indicated that the drug was well absorbed on oral administration, with median time to reach maximal plasma concentration, median T_{max} is at 1.000 hr ranging from 0.500 hrs to 2.000 hrs. The mean elimination half-life was 5.818 ± 0.47 hrs. The mean C_{max} and AUC_{0-t} were 5.724 ± 0.52 µg/mL and 40.838 ± 7.20 hr*µg/mL, respectively. The mean plasma clearance was 1.238 ± 0.22 L/hr and mean volume of distribution was 10285.52 ± 1174.32 mL. Mean cumulative percentage urinary recovery of an unchanged the compound was 69.09%.

Cohort S3 (100 mg dose)

A total 06 healthy male subjects received 100 mg dose of the compound 11

- Pharmacokinetic evaluation indicated that the drug was well absorbed on oral administration, with median time to reach maximal plasma concentration, median T_{max} is at 1.000 hr ranging from 0.500 hrs to 1.500 hrs. The mean elimination half-life was 6.275 ± 0.65 hrs. The mean C_{max} and AUC_{0-t} were 11.489 ± 1.01 µg/mL and 92.302 ± 14.90

hr* μ g/mL, respectively. The mean plasma clearance was 1.099 ± 0.15 L/hr and mean volume of distribution was 9847.576 ± 825.72 mL. Mean cumulative percentage urinary recovery of an unchanged the compound was 76.63%.

Overall, the compound 11 exhibited rapid oral absorption from gastrointestinal track with maximum concentration achieved at 1.0 to 1.5 hours. Dose-related increase in exposure (C_{max} & AUC) of the compound 11 was observed from 25 to 100 mg dose. The mean elimination half-life was about 6.0 – 6.5 h across all three doses. The majority of an unchanged the compound 11 was recovered in urine suggests that the renal is a primary route of the compound excretion.

10 Pharmacodynamic Results

Blood isolated at predose, 3, 6, 12 and 24 hours was activated ex vivo with LPS and ATP and secreted IL-1 β and IL18 was measured in LPS/ATP treated and untreated whole blood.

Descriptive statistics (n, mean, standard deviation) of the corrected IL-1 β whole blood concentration was summarized by treatment and time point. Levels of BLQ were set to 0.

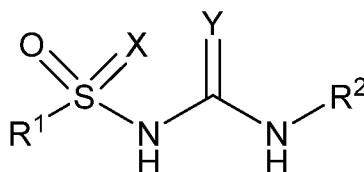
15 Corrected IL-1 β whole blood concentration was derived as: (IL-1 β concentration in treated sample - IL-1 β concentration in untreated sample).

Percentage of IL-1 β inhibition is calculated as: [(treated concentration at predose – untreated concentration at predose) - (treated concentration at Rx time point – untreated concentration at Rx time point)] / (treated concentration at predose – untreated concentration at predose) *100%.

All 17 subjects showed more than 90% inhibition of IL-1 β after the administration of compound 11. Single dose of 25 mg, 50 mg & 100 mg, the compound 11 showed ex vivo IL-1 β inhibition above 90% till 6 hrs, 12 hours & 24 hrs post dose, respectively.

We claim:

1. A method for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS), which comprises administering a compound of formula (I)



Formula (I)

or its pharmaceutically acceptable salts

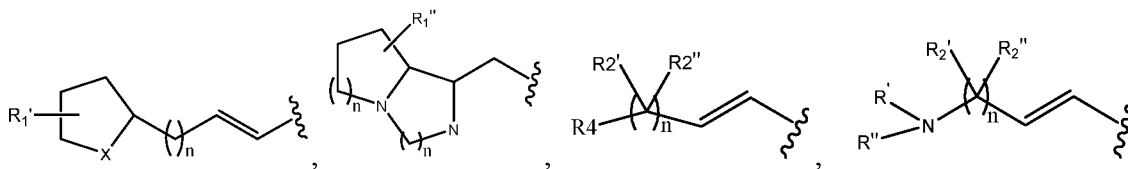
wherein

X is O, NH, or N-R³ wherein R³ at each occurrence is independently selected from hydrogen, hydroxyl, halogen, nitro, cyano, haloalkyl, optionally substituted groups selected from (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₃-C₁₀)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, SO₂(C₁-C₆)alkyl, thiol, thioalkyl, thio-alkoxy, SO(C₁-C₆)alkyl, benzyl, aryl, heteroaryl, heterocyclyl;

Y is O, S;

R¹ at each occurrence is independently selected from hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₃-C₇)cycloalkyl, (C₁-C₆)alkylSO₂(C₁-C₆)alkyl, (C₁-C₆)alkylN(C₁-C₆)alkyl, (C₁-C₆)alkylN(C₃-C₇)cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, tert-butyloxycarbonyl, NH(C₁-C₆)alkyl, N((C₁-C₆)alkyl)₂, NH(C₂-C₆)alkenyl, N((C₂-C₆)alkenyl)₂, -N-heterocyclyl, N(C₁-C₆)alkyl-heterocyclyl, NR'R'', thiol, mercaptoalkyl, SO₂(C₁-C₆)alkyl, SO₂(C₃-C₇)cycloalkyl, SO₂-aryl, SO₂-heterocyclyl, (C₁-C₆)thioalkyl, (C₁-C₆)thioalkoxy, (C₁-C₆)alkylSO₂NH₂, -CONH₂, -CO(C₁-C₆)alkyl, -CO(C₁-C₆)haloalkyl, -CO-aryl, -CO-heteroaryl, -CO-heterocyclyl, 4- to 7-membered heterocyclic ring, 7- to 14-membered bicyclic heterocyclic ring system, bridged or spiro ring system having optionally one or more than one heteroatoms;

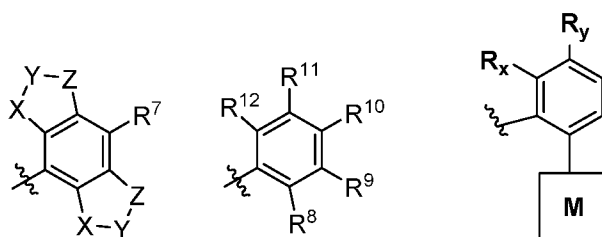
Alternatively R¹ is selected from



n , is independently selected from integer 0-3;

each of R' , R'' , R_1' , R_1'' , R_2' and R_2'' at each occurrence is independently selected from hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₃-C₇)cycloalkyl, (C₁-C₆)alkylSO₂(C₁-C₆)alkyl, (C₁-C₆)alkylN(C₁-C₆)alkyl, (C₁-C₆)alkylN(C₃-C₇)cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, tert-butylloxycarbonyl, thiol, mercaptoalkyl, SO₂(C₁-C₆)alkyl, SO₂(C₃-C₇)cycloalkyl, SO₂-aryl, SO₂-heterocyclyl, (C₁-C₆)thioalkyl, (C₁-C₆)thioalkoxy, (C₁-C₆)alkylSO₂NH₂, -CONH₂, -CO(C₁-C₆)alkyl, -CO(C₁-C₆)haloalkyl, -CO-aryl, -CO-heteroaryl, -CO-heterocyclyl, 4- to 7-membered heterocyclic ring, 7- to 14-membered bicyclic heterocyclic ring system, bridged or spiro ring system having optionally one or more than one heteroatoms; In an embodiment R' and R'' optionally forms 4- to 7-membered heterocyclic ring system.

R^2 is selected from the following ring system



wherein X, Y, Z at each occurrence independently represents C, N, S, SO₂, and O, which may be optionally substituted;

each of R^7 , R^8 , R^9 , R^{10} , R^{11} and R^{12} at each occurrence are independently selected from hydrogen, halogen, cyano, amide, sulphonamide, acyl, hydroxyl, optionally substituted groups selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, benzyl, aryl, heteroaryl, heterocyclyl; In one embodiment each of R^8

and R^9 , R^9 and R^{10} , R^{10} and R^{11} and R^{11} and R^{12} wherever possible, together may form a 4 to 7 membered saturated or partially saturated ring containing from 0-2 additional heteroatoms selected from the group consisting of N, O, and S(O)_p; p = 1-2.

5 R_x and R_y at each occurrence are independently selected from hydrogen, halogen, optionally substituted groups selected from (C₁-C₆)alkyl; Alternatively R_x and R_y together may form a 4- to 7-membered heterocyclic ring system;

'M' is selected from aryl, heteroaryl, heterocyclyl; and wherein when any of above defined group is substituted the substitutions on them are selected from those
 10 described above or may be selected from hydrogen, hydroxy, cyano, halo, haloalkyl, haloalkyloxy, alkylthio, optionally substituted group selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₁₀)cycloalkyl, C₁-C₆ alkoxy, aryl, heterocyclyl, heteroaryl, -COR₁₁, -CSR₁₁, C(O)OR₁₁, C(O)-R₁₁, -C(O)-NR₁₁R₁₂, -C(S)-NR₁₁R₁₂, -SO₂R₁₁ group, wherein each of, R₁₁ and R₁₂ is independently
 15 selected from hydrogen, optionally substituted group selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)cycloalkyl, aryl, heteroaryl, heterocyclyl groups.

2. The method as claimed in claim 1, wherein said compound of Formula (I) is selected from the group:

20 N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)-N'-cyano-4-fluoro-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide;
 N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide;
 25 (E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(thiazol-2-yl)ethanesulfonamide;
 (E)-2-(1-ethyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethanesulfonamide;

(E)-2-(1-ethyl-4-methyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide;

(R,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide;

5 (R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-methylpyrrolidin-2-yl)ethene-1-sulfonamide;

10 (S,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide;

(R,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

(S,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

15 sodium(S,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

potassium (R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

20 Sodium(R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

(E)-N'-cyano-2-((S)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide;

(E)-N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-((R)-1-methylpyrrolidin-2-yl)ethene-1-sulfonimidamide;

25 (E)-N'-cyano-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide;

N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((1S,8aR)-3,3,8a-trimethyloctahydropyrrolo[1,2-a]pyrazin-1-yl)methanesulfonamide

30 N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((4S,8aS)-2,3,3,8a-tetramethyloctahydropyrrolo[1,2-a]pyrazin-4-yl)methanesulfonamide;

(E)-3-(dimethylamino)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)prop-1-ene-1-sulfonamide;

sodium (E)-((3-(dimethylamino)-3-methylbut-1-en-1-yl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

5 (S,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

10 (R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

or pharmaceutically acceptable salts of any of the compounds above.

3. The method as claimed in claim 1, wherein therapeutically effective amount of compound of formula (I) or its pharmaceutically acceptable salt is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

4. The method as claimed in claim 1, wherein compound of formula (I) or its pharmaceutically acceptable salt is administered by oral, topical or parenteral route of administration, preferably administered by an oral route of administration.

5. The method as claimed in claim 1, wherein compound of formula (I) or its pharmaceutically acceptable salt is administered in combination with other suitable therapeutic agents.

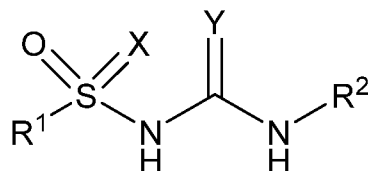
6. The method as claimed in claim 1, wherein compound of formula (I) or its pharmaceutically acceptable salt is administered in the form of pharmaceutical composition.

25 7. Use of the compound of formula (I) as claimed in claim 1 and 2 for the preparation of a medicament for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).

8. Use of the compound of formula (I) as claimed in claim 1 and 2, wherein the compound is administered in a daily dosage range is selected from 1 mg to 500 mg,

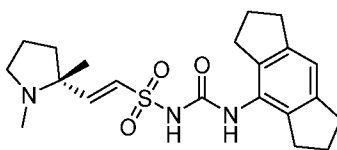
preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

9. A pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS), wherein compound of formula (I) is



Formula (I)

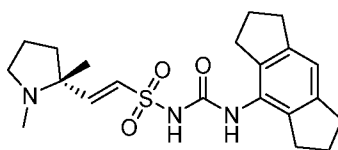
10. The pharmaceutical composition as claimed in claim 9, wherein therapeutically effective amount of compound of formula (I) or its pharmaceutically acceptable salt is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.
11. The pharmaceutical composition as claimed in claim 9 comprising compound of formula (I) and other pharmaceutically acceptable excipients for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).
12. The pharmaceutical composition as claimed in claim 9, wherein compound of formula (I) or its pharmaceutically acceptable salt is administered in combination with other suitable therapeutic agents.
13. Use of the pharmaceutical composition as claimed in claim 9 for the preparation of medicament for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).
14. A method for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS), which comprises administering a compound of formula (11)



Formula 11

or its pharmaceutically acceptable salts.

15. The method as claimed in claim 14, wherein therapeutically effective amount of compound of formula (11) or its pharmaceutically acceptable salt is selected from 1 mg to 500 mg,
5 preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.
16. The method as claimed in claim 14, wherein compound of formula (11) or its pharmaceutically acceptable salt is administered by oral, topical or parenteral route of administration, preferably administered by an oral route of administration.
- 10 17. The method as claimed in claim 14, wherein compound of formula (11) or its pharmaceutically acceptable salt is administered in combination with other suitable therapeutic agents.
18. The method as claimed in claim 14, wherein compound of formula (11) or its pharmaceutically acceptable salt is administered in the form of pharmaceutical
15 composition.
19. Use of the compound of formula (11) as claimed in any one of the preceding claims for the preparation of a medicament for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).
20. Use of the compound of formula (11) as claimed in any one of the preceding claims
20 wherein the compound is administrated in a daily dosage range is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.
21. A pharmaceutical composition comprising compound of formula (11) or its pharmaceutically acceptable salts for the treatment of Cryopyrin Associated
25 Periodic Syndromes (CAPS), wherein compound of formula (11) is



Formula (11)

22. The pharmaceutical composition as claimed in claim 21, wherein therapeutically effective amount of compound of formula (11) or its pharmaceutically acceptable salt is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.
- 5 23. The pharmaceutical composition as claimed in claim 21 comprising compound of formula (11) and other pharmaceutically acceptable excipients for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).
24. The pharmaceutical composition as claimed in claim 21, wherein compound of formula (11) or its pharmaceutically acceptable salt is administered in combination
10 with other suitable therapeutic agents.
25. Use of the pharmaceutical composition as claimed in claim 21 for the preparation of medicament for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).
- 15 26. The pharmaceutical composition as claimed in claim 21, wherein other pharmaceutically acceptable excipients are selected from diluents, carriers, binders, disintegrating agents, lubricating agents and surface active agents.
27. The pharmaceutical composition as claimed in any one of the preceding claims, wherein diluents are selected from lactose monohydrate, polymethacrylates selected from Eudragit, potassium chloride, sulfobutylether b-cyclodextrin, sodium chloride
20 and spray dried lactose and suitable combination thereof.
28. The pharmaceutical composition as claimed in as claimed in any one of the preceding claims, wherein carriers are selected from lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate and kaolin, crystalline cellulose, silicic acid and suitable combination thereof.
- 25 29. The pharmaceutical composition as claimed in as claimed in any one of the preceding claims, wherein binders are carbomers selected from carbopol, gellan, gum Arabic, hydrogenated vegetable oil, polymethacrylates selected from Eudragit, xanthan, lactose and Zein and suitable combination thereof.

30. The pharmaceutical composition as claimed in any one of the preceding claims, wherein disintegrating agents are selected from bicarbonate salt, chitin, gellan gum, polacrillin potassium, docusate sodium and suitable combination thereof.
- 5 31. The pharmaceutical composition as claimed in any one of the preceding claims, wherein lubricating agents are selected from Glycerin behenate, hydrogenated vegetable oil, sodium stearyl fumarate, myristic acid and suitable combination thereof.
- 10 32. The pharmaceutical composition as claimed in any one of the preceding claims wherein surface active agents are nonionic surfactant selected from alkyl polyglucosides, cocamide DEA, cocamide MBA, cocamide TEA, decyl maltoside and octyl glucoside; anionic surfactant selected from arachnidan acid and arachidonic acid; cationic surfactant selected from cetyl trimethylammonium bromide and cetyl pyridinium chloride and suitable combination thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/056329

A. CLASSIFICATION OF SUBJECT MATTER

A61P31/18, C07D205/04, C07C311/00 Version=2022.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K, C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2020148619A1 (CADILA HEALTHCARE LTD) 23 JULY 2020 (23-07-2020) see, abstract, claims 1, 7, 8, 10-11, examples 56, 111	7-13, 19-33

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

31-10-2022

Date of mailing of the international search report

31-10-2022

Name and mailing address of the ISA/

Indian Patent Office

Plot No.32, Sector 14, Dwarka, New Delhi-110075

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2022/056329

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-6, 14-18
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 1-6, 14-18 relates to [a method for treatment of the human, which does not require an international search by the International Searching Authority in accordance with PCT Article 17(2)(a)(i) and [Rule 39.1(iv)]].
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2022/056329

Citation	Pub.Date	Family	Pub.Date
WO 2020148619 A1	23-07-2020	CA 3126467 A1	23-07-2020
		AU 2020210117 A1	05-08-2021
		CN 113474333 A	01-10-2021
		EP 3911631 A1	24-11-2021
		US 2022169605 A1	02-06-2022